REMARKS

Claim 1 has been amended to clarify that the rodent resulting from the process of the un-amended claim, which is modified to contain a fluorescently labeled tumor is heterozygous for expression of the first fluorescent protein in all tissues except hair and erythrocytes. This characteristic is, of course, inherent in the description of the manner of producing this rodent as described in paragraph 12 and in the claim as previously proposed. The claim has also been amended simply to refer to the promoter as a promoter that effects the expression in all said tissues as is also inherent in the claim as previously proposed. The remaining changes to claim wording are to accommodate these changes. New claims 22-24 are supported by paragraph 12. No new matter has been added and entry of the amendment is respectfully requested in light of the Request for Continued Examination.

It is believed these amendments make clear the distinction between the claimed rodent and the disclosures of the art.

As background to this distinction, applicants enclose the Declaration of Dr. Robert M. Hoffman, the President of the assignee herein. As noted by Dr. Hoffman, mice or other rodents that are homozygous for the expression of the first fluorescent protein in all tissues except hair and erythrocytes are not sufficiently sturdy to be both immunocompromised and modified to contain a tumor so as to serve as a model system. Because this is the case, it is necessary to assure that the rodents to be used as such models be heterozygous for the first fluorescent protein expression system.

Before addressing the outstanding rejections, applicants will set forth the rationale behind the necessity for the method of preparation claimed in claim 22. This is shown in Exhibit 1, keeping in

mind that it is practical to identify rodent offspring with both fluorescence in all tissues and also the immunocompromised state. Nude mice are used as the example in Exhibit 1. The starting point, as set forth in the examples, is a transgenic mouse which is heterozygous for the ubiquitous expression of the first fluorescent protein. In the example set forth in the specification, the mouse of Okabe was used. This mouse is heterozygous as only a single copy of the expression system will be integrated into the fertilized egg from which the Okabe mouse is produced. Therefore, those offspring in F1 that are fluorescent will be heterozygous as well, but also will not be homozygous, as would be required, for being immunocompromised.

By crossing these fluorescent F1 offspring, offspring of the second generation (F2) are obtained where both heterozygous and homozygous ubiquitous expression in some of the offspring will be associated with being immunocompromised. (Of course, some offspring will be ff and some x/nu, but these are not further bred.)

Only the heterozygous fluorescent rodents will be useful in the tumor model system. Therefore, to assure that all of the fluorescent mice are heterozygous, the fluorescent offspring of F2 that are immunocompromised are crossed with immunocompromised mice that are not fluorescent. Therefore, in F3, all of the fluorescent offspring produced will be both heterozygous and immunocompromised, and can thus serve as the appropriate model system. That is, by virtue of the last cross to produce F3, it is assured that all of the offspring will be heterozygous and immunocompromised.

Turning, then, to the outstanding rejections, claims 1-3 were rejected as assertedly unpatentable over the combination of Okabe, *et al., FEBS Lett.* (1997) 467:313-319 in view of Kern (WO02/28188), as well as Yang, *et al., PNAS* (2002) 99:3824-3829.

The claims as now presented require that the immunocompromised mouse which shows fluorescence in all tissues must be heterozygous for the fluorescence expression system that effects this ubiquitous background fluorescence. Okabe does indeed teach such a heterozygous mouse, but which is not immunocompromised. The question then becomes whether turning to Kern, one would understand that heterozygosity is required in order to achieve the desired rodent which can serve as a model system. (Okabe states that the transgenic mice expressing GFP can be used as a model for tumors by implanting non-green tumor cells, but does not explain how this could be done. Of course, it could be done by using syngeneic tumors, but these are not particularly useful as model systems, which typically are of interest for modeling human tumors in rodents.)

Okabe clearly does not suggest that the fluorescent mice be immunocompromised which, as stated above, would be a prerequisite for modeling human tumors in rodents. Therefore, Kern is cited as teaching a transgenic animal where at least some of the tissues are fluorescent. As pointed out by the Office, Kern states that the fluorescent animal (which is not necessarily or even as disclosed fluorescent in all tissues) can be crossed with a strain of immunodeficient animals to obtain immunodeficient offspring having some fluorescent tissue.

Kern explicitly teaches away from the necessity of heterozygosity by noting that the fluorescent trait can be either homozygous or heterozygous. (There is no question of accidental anticipation – the issue is what is suggested.) This is consistent with the proposed use of Kern's animals which are only to provide tissues that are recognizably different from those that are to be isolated therefrom. In the context of Kern, since expression of the fluorescent protein need not be (and is not even suggested to be) ubiquitous, there is no need to achieve heterozygosity. This is in contrast to the presently claimed rodents where, because of the ubiquitous expression of the green

protein, heterozygosity is needed in order to permit the animal to tolerate both being immunocompromised and transplanted with a foreign tumor. It is only the present inventors who have appreciated this necessity.

Yang adds little to the basis for rejection as Yang describes only different colored tumors, not a tumor of one color against a background of another.

Basically, the rejection is in error because the combination of Okabe, Kern and Yang fail to teach that an immunocompromised ubiquitously florescent rodent to be used as a tumor model must be heterozygous for the fluorescence-generating gene.

Similar comments apply to the rejection over the combination of Okabe and Kern in view of Verkhusha, *J. Biol. Chem.* (2001) 276:29621-29624. Verkhusha teaches no more than Yang, *i.e.*, that it is possible to dual image fluorescence proteins of different colors. The combination of Okabe, Kern and Verkhusha fail to teach that using ubiquitous expression of a fluorescent protein as a background in an immunocompromised model system for tumors must employ a rodent that is heterozygous for this expression.

Conclusion

The claims have been amended to clarify the rationale for the process for preparing the claimed rodents that was set forth in the previous claims. Because the rodents are intended to be tumor models (the presence of a tumor modified to contain a protein with a different color fluorescence is required) and because the background fluorescence is ubiquitous, the rodents must be both heterozygous for the expression of the fluorescence gene in all tissues and must be immunocompromised. Only applicants understood that heterozygosity is required in this context.

Therefore, only applicants suggest a method for preparation that guarantees this. In light of the foregoing, applicants believe the rejections may be withdrawn and claims 1-3 and 22-24 passed to issue.

Should minor issues remain that could be resolved by telephone, a telephone call to the undersigned is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 312762004400.

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Respectfully submitted,

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